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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/487,841	01/19/2000	Roy A. Gravel	50004/003004	3640

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Kristina Bieker-Brady PhD
Clark & Elbing LLP
176 Federal Street
Boston, MA 02110

EXAMINER
CHEN, SHIN LIN

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 11/22/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/487,841	Gravel et al.
Examiner	**Art Unit**
Shin-Lin Chen	1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Sep 10, 2002* .

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-3 and 5-34* is/are pending in the application.

4a) Of the above, claim(s) *12 and 15-20* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-3, 5-11, 13, 14, and 21-34* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicants' amendment filed 9-10-01 has been entered. Claims 1-3 and 5 have been amended. Claim 4 has been canceled. Claims 22-34 have been added. Claims 1-3 and 5-34 are pending and claims 1-3, 5-11, 13, 14 and 21-34 are under consideration.

Claim Objections

1. Claim 3 is objected to under 37 CFR 1.75(c) as being in improper form because claim 3 depends on a latter claim 26. A claim must depend on a preceding claim but not a latter claim.

2. Claim 5 is objected to under 37 CFR 1.75(c) as being in improper form because claim 5 depends on a latter claim 26 or 28. A claim must depend on a preceding claim but not a latter claim.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-3, 5-11, 13, 14 and 21 remain rejected and claims 22-34 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for increased risk for mothers to develop neural tube defects (NTD) with combination of **homozygous** mutant MTRR genotype having an A/G polymorphism at bp 66, which yields an isoleucine (22I) or a

methionine (22M) at amino acid position 22, and low cobalamin; mothers of Down's Syndrome babies are more likely to have MTRR polymorphism of A->G at nucleotide position 66 and methylenetetrahydrofolate reductase (MTHFR) polymorphism C->T at nucleotide position 677 than control mothers; individuals having a MTRR **homozygous** 66 A->G polymorphism are at greatest risk of developing coronary artery disease (CAD) and the association of the MTRR genotype with CAD is not modulated by vitamin B12 status or MTHFR genotype (See specification page 56, 58, 63, 66, 68), and the association of homocysteine, folic acid, vitamin B6 and vitamin B12 with cancer and vascular disease as disclosed by Mayer et al., 1996 (JACC, Vol. 27, No. 3, p. 517-527), does not reasonably provide enablement for a method of preventing cancer, cardiovascular disease, Down's Syndrome, or NTD in a subject by modulating MTRR biological activity, a method of treating or preventing cardiovascular disease or any disease by using metabolite or cofactor, such as folate, cobalamin, s-adenosyl methionine, betaine or methionine with or without detecting an increased risk of developing cancer, cardiovascular disease, NTD or Down's syndrome in a test subject, a method of treating cancer, cardiovascular disease, or a NTD in a subject by using a protein, a small molecule, or an antisense nucleic acid molecule, and a method for detecting an increased risk of developing a NTD, Down's Syndrome, or cardiovascular disease in any mammalian fetus or embryo by detecting any heterozygous or homozygous MTRR polymorphism in either or both future parents of said embryo or fetus, or in said embryo or fetus. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention

commensurate in scope with these claims and is repeated for the reasons set forth in the preceding Official action mailed 3-5-01 (paper No. 8). Applicant's arguments filed 9-10-02 have been fully considered but they are not persuasive.

Claims 22-34 are newly added claims. Claims 23-25 are directed to a method of preventing cancer, cardiovascular disease, Down's Syndrome, or NTD in a subject by modulating MTRR biological activity with protein, small molecule, or antisense nucleic acid. Claims 26-32 are directed to a method of treating or preventing cardiovascular disease or any disease by using metabolite or cofactor, such as folate, cobalamin, s-adenosyl methionine, betaine or methionine. Claims 33 and 34 are directed to a method of treating cancer, cardiovascular disease, or a NTD in a subject by using a protein, a small molecule, or an antisense nucleic acid molecule.

Applicants argue that numerous examples of therapeutic agents that modulate MTRR biological activity are described in the specification, and decreased MTRR activity is associated with increased risk for cardiovascular disease, neural tube defects and cancer. Applicants further argue that compounds that increase MTRR activity are useful in the treatment and prevention of cardiovascular disease, NTD and cancer (amendment, p. 7, 8). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 3-5-01 (Paper No. 8). The specification only discloses certain homozygous MTRR polymorphism that is associated with increased risk of NTD, Down's syndrome or cardiovascular disease but fails to provide any enabling disclosure for treating or preventing any cardiovascular disease, neural tube defects, cancer, or any other disease. There is no evidence of record that any metabolite or cofactor, any

protein, small molecule or any antisense nucleic acid molecule can be used to prevent cancer, cardiovascular disease, Down's Syndrome, or NTD in a subject by modulating MTRR biological activity, or any metabolite or cofactor can be used to treat or prevent cardiovascular disease in a subject, or any protein, small molecule and any antisense nucleic acid molecule can be used to treat cancer, cardiovascular disease, or NTD in a subject *in vivo*.

The specification of the present application fails to provide adequate guidance and evidence for the correlation between the inhibition or activation of MTRR biological activity and treating or preventing cancer, cardiovascular disease, NTD or Down's Syndrome in a subject. The specification also fails to teach how to use the agent that inhibits or activates MTRR biological activity to treat or prevent the diseases set forth above. The specification fails to teach where and how to administer those agents to a subject, the dose required to provide therapeutic effects, and whether sufficient agent would be present for a sufficient duration of time at the targeted site to provide therapeutic effect in a subject *in vitro* or *in vivo* to treat or prevent the diseases set forth above. In view of such, one skilled in the art at the time of the invention would not know which agent is to be used and how to use said agent to treat or prevent the diseases set forth above, and would require undue experimentation to practice over the full scope of the invention claimed.

Applicants argue that test compounds can be screened for their ability to modulate MTRR activity and transgenic mouse model can be used to screen test compounds that modulate MTRR activity. Applicants further argue that the specification discloses numerous routes of

administration that can be used to provide sufficient amount of agent to treat or prevent cancer, cardiovascular disease, Down's syndrome, or NTD (amendment, p. 9). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 3-5-01 (Paper No. 8) and the reasons set forth above. Generation of a transgenic mouse with a particular resulting phenotype was unpredictable itself at the time of the invention. As discussed under gene therapy section, the state of the prior art of gene therapy was not well developed and was highly unpredictable at the time of the invention. The fate of the DNA vector itself, the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, the administration route of a composition containing a protein to a subject, and the protein's compartmentalization within the cell, or its secretory fate, once produced are all important factors for a successful gene delivery *in vivo*. Thus one skilled in the art at the time of the invention would have to engage in undue experimentation to practice over the fulls scope of the invention claimed.

Applicants amended claim 1 and added claim 33 to recite administration of a protein, a small molecule and an antisense nucleic acid molecule, and amended claim 2 and added new claims 26 and 27 to recite administration of a metabolite or cofactor and argue that the specification enables the claimed invention (amendment, p. 9-10). This is not found persuasive

because of the reasons set forth in the preceding Official action mailed 3-5-01 (Paper No. 8) and the reasons set forth above.

Applicants argue that alterations in the metabolism of folates, homocycteine etc. may be associated with a higher risk for cardiovascular disease and Down's syndrome, and supplying metabolites or cofactors that are downstream of MTRR activity is useful to treat or prevent the diseases associated with MTRR deficiency (amendment, p. 10-11). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 3-5-01 (Paper No. 8) and the reasons set forth above. Mere speculation of the association of alterations in the metabolism of metabolites and the risk for the disease set forth above, and of supplying metabolites or cofactors that are downstream of MTRR activity to treat or prevent the diseases associated with MTRR deficiency can not be translated to success in treating or preventing the diseases set forth above. The specification must provide sufficient enabling disclosure for the claimed invention.

Applicants argue that the specification teaches A/G polymorphism at nucleotide position 66 and 110 and such homocycteine metabolic alteration are known to result in hyperhomocysteinemia, and other polymorphisms in MTRR gene would be likely to demonstrate a similar correlation. Applicants further argue that the specification teaches that mildly elevated homocysteine level indicate a risk factor for cardiovascular disease, NTD, cancer and Down's syndrome and methods for detecting MTRR polymorphism were known and one skilled in the art can correlate the polymorphism to the risk of developing the diseases set forth above (amendment, p. 11, 12). This is not found persuasive because of the reasons set forth in the

preceding Official action mailed 3-5-01 (Paper No. 8). It was known in the art that different polymorphism or mutation within a gene could result in dramatic different effect on the function of the gene product and therefore, different correlations with increased risk of developing a NTD, Down's Syndrome, or cardiovascular disease. It was unpredictable at the time of the invention whether a polymorphism or a mutation within MTRR gene either heterozygous or homozygous would be correlated to increased risk of developing a NTD, Down's Syndrome, or cardiovascular disease. The specification fails to provide adequate guidance and evidences for any polymorphism or mutation within the MTRR gene other than the polymorphism disclosed in the specification and fails to teach the correlation of said polymorphism or mutation with increased risk of developing a NTD, Down's Syndrome, or cardiovascular disease in any mammalian fetus or embryo. Thus, one skilled in the art at the time of the invention would have to engage in undue experimentation to practice over the full scope of the invention claimed.

Applicants argue that the specification provides assays for determining whether a particular MTRR mutation results in decreased or increased MTRR biological activity, and thus is **likely** correlated with an altered risk for cardiovascular disease, NTD, Down's syndrome or cancer, and the correlation may be further examined. Applicants argue that the specification needs not teach every possible embodiment of the invention and the specification provides sufficient information such that one skilled in the art can make and use the claimed invention without undue experimentation (amendment, p. 13, 14). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 3-5-01 (Paper No. 8) and the reasons

set forth above. Mere speculation of the correlation between MTRR mutation that alters MTRR biological activity and risk for cardiovascular disease, NTD, Down's syndrome or cancer fails to provide sufficient support to enable the claimed invention. The specification must provide sufficient enabling disclosure for the claimed invention. The determination of whether a MTRR mutation that alters MTRR biological activity is correlated to the risk for cardiovascular disease, NTD, Down's syndrome or cancer requires further study and research. As discussed above, it was unpredictable at the time of the invention whether a polymorphism or a mutation within MTRR gene either heterozygous or homozygous would be correlated to increased risk of developing a NTD, Down's Syndrome, or cardiovascular disease. Thus, one skilled in the art at the time of the invention would have to engage in undue experimentation to practice over the full scope of the invention claimed.

Conclusion

No claim is allowed.

5. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. The examiner can normally be reached on Monday to Friday from 9 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds can be reached on (703) 305-4051. The fax phone number for this group is (703) 308-4242.

Questions of formal matters can be directed to the patent analyst, Patsy Zimmerman, whose telephone number is (703) 305-2758.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Shin-Lin Chen, Ph.D.